Clinical outcome of three fractionation schedules of preoperative radiotherapy for rectal cancer

Iwona WZIĘTEK, Jerzy WYDMAŃSKI, Rafal SUWIŃSKI

SUMMARY

AIM: To evaluate the effectiveness and normal tissue reactions of three fractionation schedules of preoperative radiotherapy for locally advanced rectal cancer.

MATERIALS AND METHODS: Between 1996 and 2002, 168 patients with locally advanced rectal cancer were treated as follows: 53 patients received 25 Gy in 5 Gy per fraction (group A), 45 received 30 Gy in 3.0 Gy per fraction (group B), and 70 were treated with accelerated hyperfractionation: 42 Gy, 1.5 Gy per fraction, given twice a day with an inter-fraction interval of 6 hours (group C). The clinical characteristics of the groups were comparable. The patients did not receive concurrent chemotherapy. A Cox proportional hazard regression model was used to analyze the factors which may influence loco-regional tumour control (LRC) and overall survival (OS).

RESULTS: The following variables significantly influenced LRC: fractionation scheme (5-year LRC 80%, 69%, and 90% in groups A, B, C respectively, p=0.016), haemoglobin concentration before radiotherapy (p= 0.012) and postoperative chemotherapy (p=0.01). Age, sex, stage of disease, location of tumour (distance of the tumour from the anal verge) and performance status did not appear significant for LRC. The overall 5-year OS was 64%, 59% and 74% in groups A, B, C respectively (p=0.056). The OS was significantly influenced by postoperative pathological stage (p=0.006), tumour location (p= 0.015) and postoperative chemotherapy (p=0.047). The most frequent acute radiation reaction was mild/severe diarrhoea, which appeared in 5%, 21.6% and 65.5% of the patients from groups A-C respectively. The median wound healing time in those who underwent abdomino-perineal resections was 6, 6 and 4 weeks. Other reactions appeared less relevant. There was no significant difference in the incidence of late effects among the three treatment groups.

CONCLUSION: While due to the non-randomized character of the study the conclusions should be regarded as hypothesis-generating only, the analysis has shown an acceptable local effectiveness and tolerance of schedules A and C, and disappointing effectiveness of schedule B. The present study thus supports the data which suggest that the clinical effect of preoperative radiotherapy for rectal cancer is influenced not only by total radiation dose but also by overall radiation treatment time and dose per fraction.

KEY WORDS: preoperative radiotherapy, rectal cancer, fractionation

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Department of Radiation Oncology
Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch

Address for correspondence:
Iwona Wzietek, Medical Doctor
Department of Radiation Oncology
Maria Sklodowska-Curie Memorial Cancer Centre
and Institute of Oncology,
Wybrzeze AK 15
44-101 Gliwice, Poland
iwonawzk@gmail.com

BACKGROUND

For several decades surgical resection of the primary and of the regional lymph nodes was the standard treatment for patients with rectal cancer. Recurrence following surgery has been, however, a major problem and was often the ultimate cause of death. An improvement in surgical technique allows the local recurrence rate to be decreased with surgery alone, although the reported incidence of 10–30 percent is still not satisfactory [1–4]. The next step to reduce local relapse rate and improve overall survival was combining surgery with other modalities. The value of adding radiotherapy to surgery has been assessed in trials using either preoperative or postoperative irradiation

[5, 6]. The potential advantage of postoperative irradiation is selection of patients based on pathological results and the ability to exclude patients who have metastatic disease at surgery. The main rationale for introducing preoperative irradiation is to sterilize the cells that have formed micrometastases around the primary tumour or have invaded the nearby organs. The outcomes of clinical trials suggest a benefit from preoperative treatment [5–11]. However, a large number of issues related to total radiation dose and dose per fraction still need to be resolved or further refined. A great number of diverse schedules is used in preoperative radiotherapy for locally advanced rectal cancer; these include hypofractionation, conventional fractionation and accelerated hyperfractionation [12–16]. In this study we focused on assessment of the effectiveness and acute and late toxicity of three different fractionation schedules.

AIM

To evaluate the effectiveness and normal tissue reactions of three fractionation schedules of preoperative radiotherapy for locally advanced rectal cancer. The evaluation of normal tissue reactions included an analysis of the incidence of surgical complications, as well as acute and late radiation effects.

MATERIALS AND METHODS

Between February 1996 and May 2002, 168 patients with locally advanced and histologically proven rectal cancer were treated at the Centre of Oncology, Maria Sklodowska-Curie Memorial Institute (Gliwice, Poland). All patients received preoperative external beam radiation to the primary tumour, adjacent lymph nodes and presacral region, followed by surgery. If the pathological stage was classified as Astler-Coller C, postoperative adjuvant chemotherapy was recommended. All patients had performance status 0–2 (Zubrod scale) with median age of 62 years (21–79 years). Prior to initiation of the treatment, all patients underwent a complete clinical examination and laboratory tests (blood count, renal and liver function tests, and CEA). Distant metastases were excluded by chest X-ray, abdominal ultrasound or computed tomography (CT scan). Assessment of the local extent of the tumour was evaluated by digital examination, rectal ultrasound and/or CT scan. The clinical characteristics of the groups were comparable and are summarized in Table 1.

Treatment regimens

The fractionation schemes were diversified in a non-randomized fashion into three schedules:

A) 53 patients (31%) received 25 Gy in 5 Gy per fraction
B) 45 patients (27%) received 30 Gy in 3 Gy per fraction
C) 70 patients (42%) were treated with accelerated hyperfractionation: 42 Gy, 1.5 Gy per fraction, twice a day with an inter-fraction interval of 6 hours

The details of selection criteria for a given fractionation schedule have been presented elsewhere [17]. Most of the patients in group A were admitted as inpatients for surgery before the start of radiation, whereas the patients treated with 30 Gy or 42 Gy attended radiation treatment as outpatients from home. Additionally, 18 patients from group C (10% of all patients) received prophylactic liver irradiation – 14 Gy, 1.4 Gy/fx.

Radiation therapy techniques

Between 1996 and 1998, 15 patients (9%) were treated with γ-photons using a cobalt machine (Siemens, Philips); all other patients underwent RT with 6–23-MV photons generated by a linear accelerator. According to the groups, 83% vs. 98 % and 93% of patients for groups A, B and C respectively were treated with 3D technique; the others had 2D treatment planning. Three-dimensional (3D) three-field (one posterior and two lateral fields) conformal planning technique in all cases was based on computed tomography. Patients were placed in a supine position and precise and reproducible patient immobilization was achieved with a thermoplastic mask system. Clinical target volume included the primary tumour with at least a 3 cm margin and internal iliac and presacral nodes. The lumbosacral plexus was shielded. The prescribed dose was specified according to the guidelines of the International Commission on Radiation Units Report 50 and 62, such that the reference point located at the centre of the planning target volume received

the prescribed dose, and the maximum acceptable dose inhomogeneity within the clinical target volume was 5%. Portal vision and in vivo dosimetry were used to control the referral points and the dosimetric parameters.

Surgery

The median delay between radiotherapy and surgery was 6 days and was slightly shorter in group A (3 days) compared with groups B and C (9 and 6 days, respectively). Techniques of surgery were not standardized in all patients; however, total mesorectal excision was performed in all cases. Detailed information about the type of resection and radiotherapy-surgery interval is shown in Table 2. Because the patients with rectal cancer in the lower portion were considered candidates for a sphincter-preservation trial [18], the proportion of patients who underwent anterior resection was slightly lower in group A than in groups B and C. The differences in hospital admission practice may reflect the difference in median delay between radiotherapy and surgery. However, there was no evidence in the medical records of any obvious differences in surgical procedures between groups.

Postoperative chemotherapy

Overall, 75 patients (44.6%) received postoperative adjuvant chemotherapy. In general postoperative chemotherapy was recommended for patients with Astler-Coller C stage. The regimen was bolus 5-fluorouracil (425 mg/m^2 for 5 consecutive days) and leucovorin (20 mg/m^2 for 5 consecutive days) every 4 weeks for six courses.

Evaluation of acute and late toxicities

During the preoperative treatment, patients were seen once a week for a clinical examination. Toxicity was scored at each visit according to the Dishe scale.

The evaluation of normal tissue early reactions also included an analysis of perineal wound healing time and morbidity in the perioperative period. Late toxicity was evaluated according to the RTOG/EORTC scale.

Endpoints and statistical analysis

Loco-regional control was calculated from the start of radiotherapy to the time when clinical recurrence was detected in the pelvis. Failures were defined as morphological evidence of tumour regrowth. When local recurrence and distant metastases occurred in the same patient, both types of failures were recorded, regardless of their sequence. Survival was calculated from the start of radiotherapy until the time of death from any cause or, in patients who are alive, until the time of the last follow-up. The patients were followed up at 3-month intervals for the first year, and every 6 months thereafter. Each evaluation included clinical examination, Zubrod performance status, liver function tests and CEA level. Ultrasonography of the liver and chest X-ray were performed one year after surgery or when indicated in symptomatic cases. Kaplan-Meier method was used to plot survival curves. To compare survival curves the chi-square statistic was used. In order to check if significant prognostic factors of survival exist, the Cox proportional hazard regression model was used. The significance of the Cox model was checked by chi-square test and the significance of parameters used in the Cox proportional hazard regression model was analyzed by Wald's statistic. All the statistical calculations were performed with STATISTICA (version 6.0). The difference was considered significant if the p value was less than 0.05.

RESULTS

Acute toxicity

The evaluation of normal tissue reactions included an analysis of the incidence of surgical complications, as well as of acute radiation effects. Acute toxicity was assessed using a modified Dishe scoring system (19). In 85.7% of patients from group A, 57.9% from group B and 14.3% from group C no acute reactions during radiotherapy were reported. Mild acute reactions occurred in 14.3%, 31.6% and 39.7% of the patients from groups A-C (Dishe score below 6 points); moderate reactions occurred in 0%, 7.9% and 33.3% % of the patients from groups A-C (Dishe score between 6 and 10 points); and severe reactions were noticed in 0%, 2.6% and 12.7% of the patients from groups A-C (Dishe score more then 10 points). The most frequent acute reaction during radiotherapy was diarrhoea of moderate severity, which was well controlled by diet or

Table 1. Characteristics of 168 patients with rectal cancer treated in the Centre of Oncology, Maria Sklodowska-Curie Memorial Institute – Gliwice

Characteristics	Fractionation (groups)			
	Group A 25 Gy, 5.0 Gy/fx	Group B 30 Gy, 3.0 Gy/fx	Group C 42 Gy, 1.5 Gy/fx (2 fx /day)	Total
	(N =53)	(N =45)	(N =70)	(N =168)
Age (y)				
Median	62	62	62	62
Range	21–76	37–77	45–79	21–79
Sex				
F	21 (39.6%)	18 (40.0%)	27 (38.6%)	66 (39.6%)
M	32 (60.4%)	27 (60.0%)	43 (61.4%)	102 (60.4%)
Astler-Coller c stage (stage before RT)				
B	36 (67.9%)	31 (68.9%)	46 (65.7%)	113 (67.3%)
C-D	15 (28.3%)	7 (15.6%)	23 (32.9%)	45 (26.8%)
Unknown	2 (3.8%)	7 (15.6%)	1 (1.4%)	10 (5.6%)
Astler-Coller p stage (postoperative pathologic stage)				
B	28 (52.8%)	29 (64.4%)	46 (65.7%)	103 (61.3%)
C-D	25 (47.2%)	15 (33.3%)	22 (31.4%)	62 (36.9%)
Unknown	0 (0.0%)	1 (2.2%)	2 (2.9%)	3 (1.8%)
Zubrod				
0	40 (75.5%)	21 (46.7%)	29 (41.4%)	90 (53.6%)
1-2	13 (24.5%)	24 (53.3%)	41 (58.6%)	78 (46.4%)
Distance of tumour from anal verge				
Median	6 cm	5 cm	7 cm	7 cm
≤ 6	28 (52.8%)	24 (53.3%)	14 (20.0%)	66 (39.3%)
>6	21 (39.6%)	16 (35.6%)	50 (71.4%)	87 (51.8%)
Unknown	4 (7.6%)	5 (11.1%)	6 (8.6%)	15 (8.9%)
Overall treatment time (days)				
Median	6	14	20	14
Range	5–9	11–21	18–29	5–29
Postoperative chemotherapy				
Yes	26 (49.1%)	21 (46.7%)	28 (40.0%)	75 (44.6%)
No	27 (50.9%)	24 (53.3%)	42 (60.0%)	93 (55.4%)
Haemoglobin concentration before RT (g/dL)				
Median	13.0	13.7	13.3	13.4
Range	(7.2–15.7)	(8.0–16.0)	(9.4–16.7)	(7.2–16.7)

anti-diarrhoeal medication (it appeared in 5%, 21.6% and 65.5% of the patients from groups A-C). No patient developed severe radiation dermatitis. No patient required treatment interruption. Detailed information about toxicity of treatment in patients with prophylactic liver irradiation has been described elsewhere (16). Acute postoperative morbidity was characterized by wound-healing delay. The median wound healing time in those who underwent abdomino-perineal resections was 6, 6 and 4 weeks. There was, however, no statistical difference in incidence of perineal wound infections (20.0% vs. 15.0% vs. 16.4%, groups A-C respectively). Anastomotic leakage appeared in less than 2% of all cases. Spastic ileus appeared in the perioperative period in 2 (3.8%) patients from group A (one of them had to be reoperated on). Adding prophylactic liver irradiation to preoperative radiotherapy in the group with accelerated hyperfractionation did not increase the incidence of acute toxic ef-

Table 2. Characteristics of the type of resection and radiotherapy-surgery interval in 168 patients treated with preoperative radiotherapy

Characteristics	Fractionation (groups)			
	Group A 25 Gy, 5.0 Gy/fx	Group B 30 Gy, 3.0 Gy/fx	Group C 42 Gy, 1.5 Gy/fx (2 fx /day)	Total
Type of resection				
Anterior	22 (41.5%)	23 (51.1%)	43 (61.4%)	88 (52.4%)
Abdominoperineal	27 (50.9%)	21 (46.7%)	25 (35.7%)	73 (43.5%)
Hartmann's	4 (7.5%)	1 (2.2%)	2 (2.9 %)	7 (4.2%)
Surgery-radiotherapy interval (days)				
Median	3	9	6	6
Range	1–20	1–33	2–30	1–33

fects and did not affect the rates of adherence to postoperative chemotherapy. There was no death from toxic effects.

Loco-regional control

The loco-regional control rate at five years was 81% in the study population of 168 patients. In the univariate analyses, treatment group assignment (p=0.016) (Fig. 1), haemoglobin concentration before radiotherapy (p= 0.012) and postoperative chemotherapy (p=0.01) were significant predictors of the risk of loco-regional recurrence. Patients who had postoperative chemotherapy were at higher risk for recurrence, which can be attributed to selection criteria for this therapy. Age, sex, stage of disease, location of tumour (distance of the tumour from the anal verge), performance status and type of operation did not appear to significantly influence LRC (Table 3). In a multivariate Cox regression analysis haemoglobin concentration before radiotherapy (p= 0.009) and fractionation scheme (p=0.008) appeared as independent predictors of the risk of loco-regional recurrence, whereas adjuvant chemotherapy had no independent prognostic value with respect to this endpoint (p>0.05).

Metastases-free survival

In the present study, the 5-year cumulative incidence of distant metastases was 34.0% for patients in group A, 32% and 35% in groups B and C respectively. The most common sites of metastases were the liver (17.3%) and lungs (16.7%). Interestingly, in the subgroup of patients with prophylactic liver irradiation none of the patients had liver metastases. The fractionation scheme did not influence metastases-free survival (Fig. 2). Other variables such as age, sex, clinical stage of disease, distance of the tumour from the anal verge, performance status and type of operation also did not significantly influence MFS (Table 3). However, in a univariate analysis it was significantly influenced by postoperative pathological stage and adjuvant chemotherapy. In patients who received chemotherapy this can be attributed to selection criteria for this therapy, since it was given only to patients with Astler-Coller stage C.

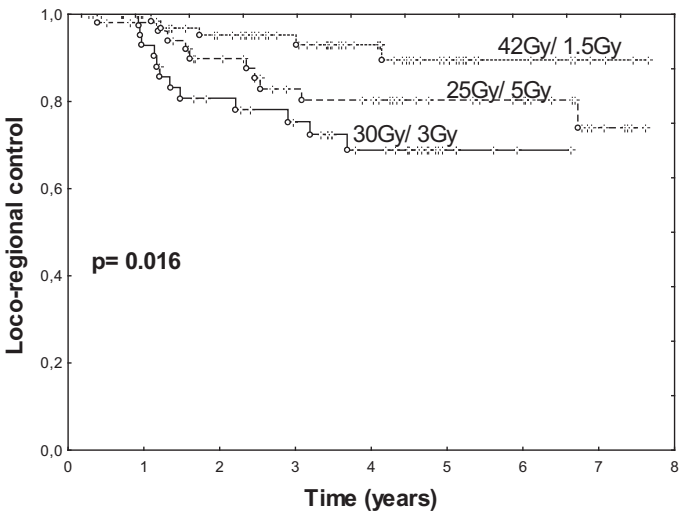

Fig. 1. Loco-regional control according to fractionation schedule. The difference in outcomes is statistically significant

Table 3. Prognostic factors influencing actuarial rates of local recurrence, distant metastases and overall survival

Characteristics	5-year LRC	p	5-year MFS	p	5-year OS	p
Fractionation scheme						
A	80		66		64	
B	69		61		59	
C	90	0.016	62	0.8	74	0.056
Age (y)						
≤ 62	84		66		73	
>62	77	0.74	60	0.66	60	0.14
Sex						
F	79		64		63	
M	83	0.42	63	0.9	68	0.78
Astler-Coller c stage(stage before RT)						
B	85		67		69	
C-D	72	0.11	58	0.94	65	0.82
Astler-Coller p stage(postoperative pathologic stage)						
B	85		73		75	
C-D	72	0.07	51	0.0004	54	0.006
Zubrod						
0	79		66		70	
1-2	84	0.71	62	0.19	60	0.24
Distance of tumour from anal vergeMedian						
≤ 6	77		67		59	
>6	86	0.16	66	0.73	75	0.015
Postoperative chemotherapy						
Yes	74		47		59	
No	90	0.01	81	0.0006	76	0.047
Haemoglobin concentration before RT (g/dL)						
≤ 13	67		55		60	
>13	91	0.012	73	0.13	75	0.085
Type of resection						
Anterior	86		65		71	
Abdominoperineal	76		62		64	0.3
Hartmann's	62	0.1	38	0.2	69	

Overall survival

The median follow-up for surviving patients was 5.2 years (95% confidence interval 4.95-5.62). The 5-year overall survival rate was 64%, 59% and 74% in groups A, B, C respectively (p=0.056). The overall survival time according to the fractionation scheme is shown in Figure 3. In the univariate analyses postoperative pathological stage (p=0.006), distance of the tumour from the anal verge (p= 0.015) and postoperative chemotherapy (p=0.047) significantly influenced OS. By contrast, fractionation scheme, age, sex, clinical stage of disease, performance status, haemoglobin concentration before the treatment and type of operation did not significantly influence OS (Table 3). A multivariate Cox regression model revealed that tumour location had an independent and significant influence on survival (p=0.04).

Late reactions

Among the patients in whom sphincter-sparing surgery was performed, 19.3% reported some form of faecal incontinence; 1 patient from group A required persistent use of pads for this complication. The incidence of perineal-vaginal fistulas in the whole group of women

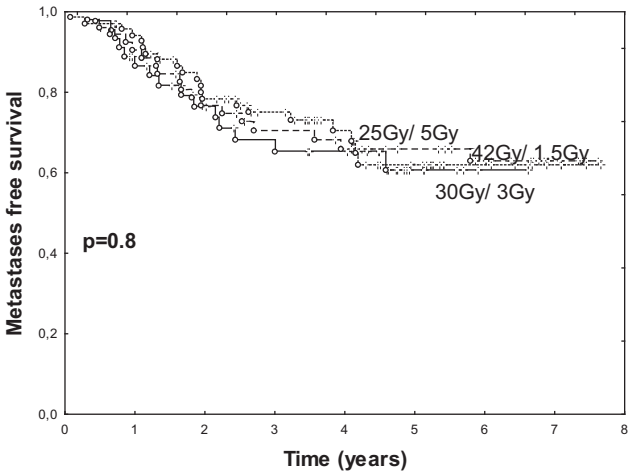

Fig. 2. Metastases-free survival according to fractionation scheme. The difference in outcomes is not statistically significant

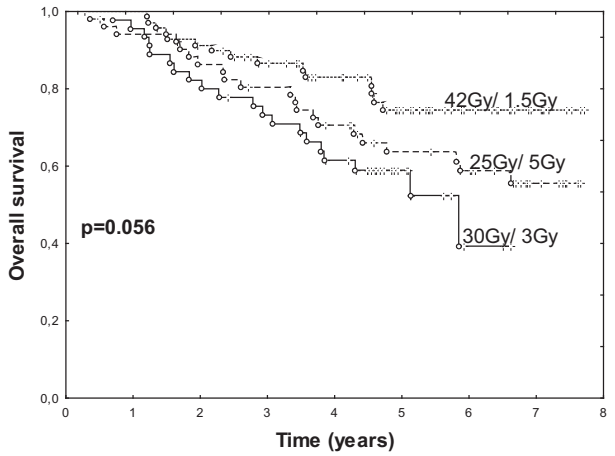

Fig. 3. Overall survival time according to fractionation scheme. The difference in outcomes is statistically significant

with sphincter sparing surgery was 5.3%. In those who underwent abdomino-perineal resections, a delay in healing of the wound longer than three months was observed in 14.8%, 13.7% and 7.4% of patients from groups A-C respectively. Detailed information about frequency of late effects in each group (incidence of faecal incontinence, diarrhoea, constipation and perineal-vaginal fistulas) is shown in Table 4. One year after treatment two patients from group A underwent unsuccessful reconstruction of the digestive tract complicated by necrosis of the small bowel in the region of the anastomosis. However, there was no significant difference in the incidence of late effects among the three treatment groups.

DISCUSSION

Radiation morbidity is as important as tumour control when determining the value of a given fractionation schedule. Thus, in this study, we evaluated the efficacy and toxicity of three different fractionation schedules of preoperative radiotherapy in patients with resectable rectal cancer. In general, all three schedules of preoperative radiotherapy were well tolerated. There was higher incidence of mild/severe diarrhoea during radiotherapy in schedule C compared to A and B. This can be explained by the duration of radiation therapy, which was shorter in schedules A and B than the usual time required for appearance of clinical symptoms related to acute reaction. In schedule C the overall duration of radiation therapy (about 3 weeks) was long enough for symptoms to become clinically apparent. By

Table 4. Incidence of late normal tissue reactions in 168 patients with rectal cancer treated with preoperative radiotherapy

Characteristics	Fractionation (groups)		
	Group A 25 Gy, 5.0 Gy/fx	Group B 30 Gy, 3.0 Gy/fx	Group C 42 Gy, 1.5 Gy/fx (2 fx /day)
Incidence of faecal incontinence[a]	9.1%	5.9%	8.6%
Perineal-vaginal fistulas[b]	4.8%	5.9%	5.3%
Large healing delay[c]	14.8%	13.7%	7.4%
Diarrhoea	5.9%	5.0%	10.2%
Constipation	2.0%	0.0%	6.8%

[a] Analysis included only patients in whom sphincter-sparing surgery was performed.
[b] Analysis included only women in whom sphincter-sparing surgery was performed.
[c] Delay in healing of the wound longer than three months among patients after abdomino-perineal resection.

contrast, the incidence of perioperative morbidity and the incidence of late effects were slightly lower in group C compared to groups A and B. There was also slightly longer wound healing time in schedule A. This can be explained by differences in fraction doses, which were lower in schedule C compared to A and B, which could contribute to sparing of late responding tissues in schedule C.

The fractionation of preoperative radiotherapy had a significant influence on loco-regional control not only in univariate but also in multivariate analysis. While due to the non-randomized character of the study the conclusions should be drawn with caution, the analysis has shown an acceptable local effectiveness and tolerance of schedules A and C, and disappointing effectiveness of schedule B. The present study thus supports the data which suggest that the clinical effect of preoperative radiotherapy for rectal cancer is influenced not only by total radiation dose but also by overall radiation treatment time and dose per fraction. The presented data were used in an exploratory attempt to estimate the α/β ratio for rectal cancer [17]. Suwinski et al. have estimated that the α/β ratio for rectal cancer is 5.06 Gy. The normalized equivalent dose (LQED 2 Gy) for schedules A, B, C was 35.7 Gy, 34.2 Gy and 39.0 Gy respectively. The biological effect of the hyperfractionation schedule could be additionally affected by incomplete repair in tumour cells, which might happen between fractions given with a minimum 6-h interval (20). This may provide an explanation of the highest local efficiency of schedule C.

For patients with positive postoperative pathological nodal stage the risk of distant metastases was significantly higher than in the group of patients with negative lymph nodes. In our study, the 5-year cumulative incidence of distant metastases was about two times that of local recurrences and had a significant impact on OS. This may indicate that eradicating micrometastases would be a key strategy for future novel therapies for rectal cancer.

The local effect of radiotherapy was of the same magnitude regardless of the location of the tumour in the rectum. However, the survival benefit was seen in patients in whom the distance of the tumour from the anal verge was longer than 6 cm, with negative pathological nodal stage. The paradoxical effect of chemotherapy can be attributed to selection criteria for this therapy. It was given only to patients with pathological Astler-Coller stage C.

Several studies have emphasized that haemoglobin concentration is a well-recognized prognostic factor, which influences treatment outcome. This was also confirmed in our study; haemoglobin concentration before the treatment significantly influenced loco-regional control.

The non-randomized selection of patients for a given fractionation schedule limits the strengths of conclusions from the present study. Clearly, however, the present analysis suggests the necessity for further clinical research in a randomized fashion to assess more precisely the real impact of the type of preoperative radiotherapy on the effect and tolerance of combined treatment.

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